2019-08

Trends in phenotype in the English paediatric neurofibromatosis type 2 cohort stratified by genetic severity

Halliday, D

10.1111/cge.13551
Clinical Genetics: an international journal of genetics and molecular medicine
Wiley

Received: 23 November 2018 | Revised: 3 April 2019 | Accepted: 7 April 2019

DOI: 10.1111/cge.13551

ORIGINAL ARTICLE

CLINICAL GENETICS WILEY

Trends in phenotype in the English paediatric neurofibromatosis type 2 cohort stratified by genetic severity

Dorothy Halliday[1,2] | Beatrice Emmanouil[2,3] | Grace Vassallo[4] | Karine Lascelles[5] | James Nicholson[6] | Saleel Chandratre[7] | Geetha Anand[8] | Martin Wasik[9] | Pieter Pretorius[10] | D. Gareth Evans[11] | Allyson Parry[2,12] | On behalf of the English NF2 research group

[1]Oxford Centre for Genomic Medicine, Oxford University Hospitals NHS Trust, Oxford, UK

[2]Oxford NF2 Unit, Oxford University Hospitals NHS Trust, Oxford, UK

[3]Oxford Brookes University, Faculty of Health and Life Sciences, Department of Psychology, Health and Professional Development, Oxford, UK

[4]Department of Paediatric Neurology, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK

[5]Department of Paediatric Neurology, Guy's and St Thomas' NHS Foundation Trust, London, UK

[6]Department of Paediatric Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[7]Department of Paediatric Neurology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[8]Department of Paediatrics, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[9]Department of Ophthalmology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[10]Depatment of Neuroradiology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[11]Genomic Medicine, Division of Evolution and Genomic Sciences, MAHSC, University of Manchester, St Mary's Hospital, Manchester, UK

[12]Department of Neurosciences, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Correspondence
Dorothy Halliday, Oxford Centre for Genomic Medicine, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Trust,

Abstract

Childhood onset neurofibromatosis type 2 can be severe and genotype dependent. We present a retrospective phenotypic analysis of all ascertained children in England <age 18 (*N* = 87; male 61%). Mean age at last review was 13.9 years with mean follow-up 6.5 years. Patients were stratified using a validated score (1A/1B:no *NF2* pathogenic_variant in blood; 2A/2B:mild/moderate *NF2* constitutional or mosaic pathogenic_variant in blood; 3: constitutional truncating exon 2-13 pathogenic_variant. A total of 91% patients had a constitutional *NF2* pathogenic_variant (44% de novo). Mean age at first manifestation was 4.3 and 8.8 years in groups 3 and 2A, respectively. Bilateral vestibular schwannoma, intracranial meningioma and spinal schwannoma occurred in 77%, 52% and 65% of group 3 patients, respectively, and 58%, 26% and 33% in 2A. A total of 43% group 3 and 18% 2A had severe unilateral visual loss (logmar >1.0). Focal cortical dysplasia occurred in 26% group 3 and 4% 2A. A total of 48% of group 3 underwent ≥1 major intervention (intracranial/spinal surgery/Bevacizumab/radiotherapy) compared to 35% of 2A; with 23% group 3 undergoing spinal surgery (schwannoma/ependymoma/meningioma resection) compared to 4% of 2A. Mean age starting Bevacizumab was 12.7 in group 3 and 14.9 years in 2A. In conclusion, group 3 phenotype manifests earlier with greater tumour load, poorer visual outcomes and more intervention.

KEYWORDS

childhood NF2, NF2, NF2 genetic severity score, paediatric NF2 genotype phenotype

D Gareth Evans and Allyson Parry joint contributed for this study.

Windmill Road, Oxford, UK.
Email: dorothy.halliday@ouh.nhs.uk

Funding information
Biomedical Research Centre, Grant/Award Number: IS-BRC-1215-20007

1 | INTRODUCTION

Neurofibromatosis type 2 (NF2) can be a severe debilitating condition, particularly if the onset is under the age of 18. It is caused by pathogenic variants (path_variants) in the *NF2* tumour suppressor gene on chromosome 22[1] and has a birth incidence of 1 in 25-33000.[2] NF2 is characterised by the development of multiple neurological tumours; typically bilateral vestibular schwannoma (VS), cranial and spinal meningioma, other intracranial, spinal and peripheral nerve schwannoma and spinal ependymoma.[3,4] Clinical manifestations can include hearing and visual loss, peripheral mononeuropathy and cranial nerve palsy.[3,5-7] The severity spectrum ranges from incidentally detected disease in older adults,[8] to severe disease presenting in infancy.[9] While adults typically present with VS-related symptoms such as hearing loss or tinnitus[5] children predominantly present with non-vestibular manifestations related to eye or skin features, or signs suggesting a cranial nerve palsy (CNP), cranial meningioma or spinal tumour.[7,10-14] Younger age at first manifestation often indicates increased severity and poorer prognosis and survival.[15]

While NF2 presenting in later life may cause minor morbidity; childhood onset NF2 often needs frequent intervention, causes significant disability, and reduces quality and length of life.[3,15-18] Affecting severity is the nature and extent of the *NF2* path_variant.[19-22] Most severely affected are those with constitutional truncating path_variants between exons 2-13[22-25]; in contrast constitutional missense or splice-site path_variants, or mosaic path_variants cause milder disease.[23,24,26-29] Those affected mildly, although suffering hearing loss, often live a full lifespan, work and reproduce. Those with severe phenotypes, with impaired mobility, vision and hearing, have lower reproductive fitness and less commonly undertake paid employment.[30]

Management aims to maintain function and slow progression[3,31,32] but is complicated due to fear of radiation induced malignancy,[33] neurosurgical morbidity and Bevacizumab induced hypertension and proteinuria.[34,35] Other agents including Everolimus have been tried but evidence on efficacy and safety is limited.[36] Natural history NF2 data utilising current management is important, to inform management options.

Natural history NF2 studies refer to three phenotypes; mild adult-onset Gardner NF2, severe Wishart pre-pubertal NF2, and the earliest-onset congenital form.[9,32,37] Other studies divided patients into milder and severe phenotypes according to number of lesions or age of onset.[38] Many studies assess the whole cohort together, making extrapolation for individual patients difficult.[39-41] The UK-NF2 genetic severity score was devised and validated[42] to integrate molecular data into clinical use and to facilitate collation of genotype stratified natural history data.

NF2 care in England (population 53.5 million) has been centralised since 2010 and is co-ordinated through four centres (Cambridge, London, Oxford and Manchester).[43] Care for all children with NF2 in England is managed through the NF2 service. We have reviewed the notes of all affected children known to the service. By stratifying phenotypic data by genotype the aim is to better understand NF2 natural history to aid management decisions.

2 | SUBJECTS AND METHODS

All children in England diagnosed with NF2 using the Manchester criteria[5] or with a pathogenic *NF2* variant, aged under 18 by April 2016 and cared for through the English NF2 service were included in the study. NF2 records held within the four NF2 centres were reviewed primarily by DH, AP and KL, and an anonymised retrospective data collection proforma completed for each patient.

Patients were stratified using the previously published and validated UK genetic severity score[42](Table 1) and data analysed for trends. Briefly, 1A/1B represents where no *NF2* path_variant was detected in blood, 2A and 2B represents a mild or moderate, respectively, constitutional or mosaic *NF2* path_variant detected in blood and 3 represents those with a constitutional truncating path_variant within exons 2-13.

SPSS 23 (Guilford, Surrey, UK) was used for all statistical analyses. Genetic severity was treated as an ordinal variable. We reported standard summary statistics throughout with statistical significance of inferences set to 5%. Directions in trends and associations were hypothesised to reflect an increased clinical severity with genetic severity score. Trends in demographics, clinical phenotype, interventions, and MRI features with genetic severity were investigated using Mantel-Haenszellinear-by-linearχ^2 tests of association. Associations between scalar and ordinal variables, and where necessary controlling for possible confounders, were investigated using Spearman's correlations, and where appropriate partial Spearman's correlations, after visually confirming monotonic relationships of the variables using scatterplots. Annual VS growth was calculated for all ears in each genetic severity group for which scans existed for Bevacizumab-free periods of one or more years. *T* tests were used for pairwise comparisons; inspection of outliers in the pairwise differences revealed they were not extreme and did not unduly influence the results and they were therefore kept in the analysis. All statistical comparisons were based on a-priory

TABLE 1 Genetic Severity score

NF2 pathogenic variant detected in blood			2A Mild	2B Moderate	3 Severe
Truncating pathogenic variant					
Exon 2-13 constitutional					3
Mosaic				2B	
Exon 14-15 Constitutional				2B	
mosaic			2A		
Exon 1 constitutional/mosaic			2A		
Splice site pathogenic variant					
Exon 1–7 constitutional				2B	
mosaic			2A		
Exon 8-15 constitutional			2A		
mosaic			2A		
Large Deletion excluding promotor or exon 1 constitutional				2B	
Large Deletion excluding promotor or exon 1 mosaic			2A		
Large Deletion Including promotor or exon 1 constitutional or mosaic			2A		
Small in-frame deletion or duplication constitutional or mosaic			2A		
Missense mutation constitutional or mosaic			2A		
No *NF2* pathogenic variant detected in blood	**1A**	**1B**			
Meets clinical criteria for NF2 and an identical *NF2* pathogenic variant is identified in two separate tumour samples		1B			
Meets clinical criteria for NF2 but analysis of two tumours is not available to confirm diagnosis	1A				

Data in Table 1 are reproduced from Table 1 and Table 2, in Halliday et al.[42]

hypotheses and type I error rate was controlled using the Benjamini-Hochberg procedure.

The study was approved by the National Research Ethics Service (NRES) Committee-South-West (12/SW/0042) and all procedures undertaken in the study were in accordance with the 1964 Helsinki declaration. As there was no active human participation in this study (as a retrospective, anonymised review of routinely collected clinical data), no consent was deemed necessary by the NRES committee.

3 | RESULTS

3.1 | Patient demographics

Notes of 87 children (male 53, 61%) were reviewed. Mean age at data collection was 13.9 years and mean length of follow up 6.5 years. Table 2 shows the proportions within each genetic severity group with mean current age, length of follow up, age of diagnosis, age at first manifestation, the proportion having presymptomatic or diagnostic genetic testing and those with familial (56%) or sporadic (44%) disease. Presymptomatic testing was more common in group 2A (46%) and less common with increasing genetic severity (2B 20% and group 3 19%, $P = .011$). Patients with sporadic disease were more commonly group 3 (18/38 47%) compared to 2A (6/38 16%); in contrast familial NF2 patients were more commonly 2A (20/49 41%) than group 3 (13/49 27%; $P = .003$). Mean age at first manifestation was 4.3 years in group 3 compared to 8.8 years in group 2A ($P = .002$, Table 2). Only 12 (41%) familial patients in groups 2B/3 had predictive genetic testing as NF2 clinical features were already apparent in the remainder before testing.

3.2 | Molecular profile

No cases were assigned 1A/1B as all cases had an *NF2* path_variant identified in blood (75/87 86% constitutional, 8/87 9% mosaic) or had familial NF2 with the assumption of a constitutional unidentified *NF2* path_variant (4/87 5%, Table 2).

3.3 | Clinical phenotype

3.3.1 | Timing of first manifestation of NF2

In 70% of group 2A, the initial manifestation was VS/other intracranial lesions on scan, at a mean age of 12.0. In group 3 initial manifestations were more commonly eye problems (59% at mean age 3.2) including reduced acuity, squint, cataract or ocular CNP; skin features (21% at mean age 4.5) and spinal problems (17% at mean age 9.6) with intracranial lesions documented at the time of first manifestations in 28%

TABLE 2 Cohort characteristics: demographic and molecular data

	2A Mild		2B Moderate		3 Severe		Overall	
	N = 26 (29.9%)		*N* = 30 (34.5%)		*N* = 31 (35.6%)		*N* = 87 (100%)	
	N	Column %	*N*	Column %	*N*	Column %	*N*	Column %
*Pathogenic variant:**								
Familial	20	77%	16	53%	13	42%	49	56%
Sporadic	6	23%	14	47%	18	58%	38	44%
*Type of genetic test:**								
Presymptomatic	12	46%	6	20%	6	19%	24	28%
Diagnostic	14	54%	24	80%	25	81%	63	72%
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Years of follow-up	6.0	4.5	7.1	4.8	6.2	3.9	6.5	4.4
Age of confirmed NF2 Diagnosis	8.0	5.3	7.9	5.4	6.7	5.2	7.5	5.3
Age at presymptomatic test	8.5	5.5	5.4	5.5	3.4	4.9	6.2	5.6
Age at diagnostic test	7.6	5.3	9.5	4.8	7.6	5.0	8.2	5.0
Age of first manifestation*	8.8	6.1	7.3	4.5	4.3	3.8	6.6	5.1
Age at last review	14.0	4.6	15.0	3.5	12.9	4.6	13.9	4.3
Pathogenic variant								
Mosaic in blood	**3**	**12%**	**5**	**16%**			**8**	**9%**
Constitutional variants								
Nonsense	0	0%	0	0%	14	45%	**14**	16%
Frameshift	2	8%	3	10%	17	55%	**22**	25%
Splicing	4	15%	17	68%	–	–	**21**	24%
Large deletion	6	23%	5	17%	–	–	**11**	13%
Missense	5	19%	–	–	–	–	**5**	6%
Small in-frame deletion	0	0%	–	–	–	–	**0**	0%
Chromosomal deletion	2	8%	–	–	–	–	**2**	2%
Familial NF2 (no *NF2* mutation)	4	15%	–	–	–	–	**4**	5%
Total constitutional	**23**	**88%**	**25**	**84%**	**31**	**100%**	**79**	**91%**

*$P < .05$.

(at mean age 7.8, Table 3). While 11.5% 2A patients were yet to manifest NF2 features at last review (mean age 11 years), only 6.5% group 3 were yet to manifest at mean age 4 years.

3.3.2 | Dermatological features

A significant trend was noted for presence of NF2 skin features (including NF2 plaques, subcutaneous schwannomas, pigmented and depigmented lesions) rising from 39% of 2A to 71% of group 3 (Table 4). Features were analysed jointly due to likely under ascertainment in a retrospective review.

3.3.3 | Neurological features

Cranial Nerve Palsy occurred in 26% (Table 4) affecting all three severity groups. A total of 7/87 (8%) patients had a third CNP; in one case transient before becoming permanent, and in another case bilateral. Three cases each had fourth or sixth CNP with 15/87 (17%) having an ocular CNP. Facial palsy occurred in 7/87 (8%) children; in two apparent before age 2 and in the remainder noted after age 11. In two cases (one young onset) a facial nerve schwannoma/enhancement was seen and in 5 an ipsilateral VS was noted (size 12-35 mm). A total of 7/87 (8%) cases had involvement of the lower cranial nerves; with stridor/dysphonia, uni/bilateral vocal cord palsy, or vagal/hypoglossal nerve palsy. Peripheral mononeuropathy occurred in 9 cases affecting both upper and lower limbs; 1/26 2A cases (4%) and 4/30 (14.3%) and 4/31 (12.9%) 2B and 3 cases, respectively. Two cases had finger weakness, one had ulnar distribution wasting, one had arm wasting from a brachial plexus lesion, one had unilateral weakness of foot dorsiflexion, two had quadriceps wasting (one from an L3/4 lesion), one had long standing unilateral arm and leg weakness.

A significant association was seen with severity and proportion having one or more seizures ($P = .03$, Table 4). Mean age of first

TABLE 3 First manifestations of NF2 related to genetic severity group, detailing NF2 related features that were documented, or detected on imaging, at the time of first clinical assessment

		2A Mild		2B Moderate		3 Severe		Overall	
No manifestation at last review[ba]	*N* (% of total column)	3	11.5%	4	13.3%	2	6.5%	9	10.3%
	Age at last review (M, SD)	11.0	7.8	15.0	1.8	4.0[a]	.0	11.2	6.1
		First manifestation: *Multiple manifestations per patient possible, N = 78*							
Eye problems	*N*, column %	5	22%	14	54%	17	59%	36	46%
	Age at manifestation (M, SD)	1.4	2.6	7.0	4.9	3.2	3.1	4.4	4.3
Skin problems	*N*, column %	2	9%	5	19%	6	21%	13	17%
	Age (Mean, SD)	14.0	5.7	7.8	3.4	4.5	3.2	7.2	4.7
Head lesions, of which:	*N*, column %	16	70%	11	42%	8	28%	35	45%
	Age (Mean, SD)	12.0	4.0	10.4	3.6	7.8	4.8	10.5	4.3
—VS	*N*, column %	12	52%	8	31%	5	17%	25	32%
	Age (Mean, SD)	13.1	3.0	11.1	3.2	9.4	4.9	11.7	3.6
—meningioma	*N*, column %	1	4%	6	23%	1	3%	8	10%
	Age (Mean, SD)	2.0	–	9.2	4.4	10.0	–	8.4	4.5
—other head lesion	*N*, column %	2	9%	5	19%	2	7%	9	12%
	Age (Mean, SD)	10.5	.7	12.0	2.0	3.0	1.4	9.7	4.1
Spinal lesions	*N*, column %	1	4%	2	8%	5	17%	8	10%
	Age (Mean, SD)	18.0	–	7.0	1.4	9.6	3.0	10.0	4.2
Motor function problems	*N*, column %	3	12%	2	8%	4	14%	9	10%
	Age (Mean, SD)	8.0	8.0	4.0	2.8	6.3	4.6	6.1	4.8
Neuropathy	*N*, column %	0	0%	1	4%	1	3%	2	3%
	Age (Mean, SD)	–	–	10.0	–	14.0	–	12.0	2.8
Cranial nerve palsy	*N*, column %	0	0%	1	4%	1	3%	2	3%
	Age (Mean, SD)	–	–	6.8	4.6	2.0	1.4	6.4	5.2
Raised intracranial pressure	*N*, column %	0	0%	1	4%	2	7%	3	4%
	Age (Mean, SD)	–	–	15.0	–	5.5	4.9	8.7	6.5
Developmental delay	*N*, column %	2	9%	0	0%	0	0%	2	3%
	Age (Mean, SD)	1.5	.7	–	–	–	–	1.5	.7
Hearing problems	*N*, column %	1	4%	0	0%	1	3%	2	3%
	Age (Mean, SD)	14.0	–	–	–	5.0	–	9.5	6.4
Epilepsy/seizures	*N*, column %	0	0%	2	8%	0	0%	2	3%
	Age (Mean, SD)	–	–	2.0	1.4	–	–	2.0	1.4
Cortical dysplasia	*N*, column %	0	0%	1	4%	1	3%	2	3%
	Age (Mean, SD)	–	–	3.0	–	10.0	–	6.5	4.9
Pes cavus	*N*, column %	0	0%	1	4%	0	0%	1	1%
	Age (Mean, SD)	–	–	10.0	–	–	–	10.0	–

For children diagnosed through predictive genetic testing this may have been first NF2 features noted on routine surveillance imaging. For children presenting symptomatically, the table includes all features clinically documented or identified on scan at the time of the initial presentation.

[a]$t(28) = 12.56$, $P < .001$, the severe patients who have not manifested were significantly younger at last review compared to severe patients who have manifested ($M = 13.5$, SD = 4.1).

[b]Eye problems specified included: visual impairment or loss, squint, optic nerve hypoplasia and blindness, cataracts, retinal hamartoma, amblyopia, field defect, ptosis, 3rd nerve palsy. Skin problems specified included: NF2 plaques, pigmented or depigmented patches and subcutaneous schwannomas. Other head problems specified included: Non-vestibular intracranial schwannoma (*N* = 5), gingival lump (*N* = 1), pharynx schwannoma (*N* = 1), low grade glioma/hamartoma (*N* = 1), cochlear nerve schwannoma (*N* = 1). Spinal lesions specified included: spinal ependymoma (*N* = 1), spinal meningioma (*N* = 2) and spinal schwannoma (*N* = 6), extradural schwannoma (*N* = 1), spinal lesion (unspecified, *N* = 1). Motor function problems specified included: abnormalities with gait (*N* = 5), weakness (*N* = 1), foot drop (*N* = 1), leg wasting (*N* = 1), upper motor neuron (*N* = 1). Developmental delay included 2 severe/global developmental delay cases: 1 secondary to chromosome 22 microdeletion and 1 ring chromosome 22.

TABLE 4 Clinical phenotype of NF2

	2A Mild		2B Moderate		3 Severe		Overall	
	N = 26 (29.9%)		*N* = 30 (34.5%)		*N* = 31 (35.6%)		*N* = 87 (100%)	
	N	Column %	*N*	Column %	*N*	Column %	*N*	Column %
NF2 skin features (*N* = 75)*	7	39%	18	62%	20	71%	45	60%
Neurological features								
Seizures* (*N* = 84)	0	0%	2	7%	6	19%	8	9%
Cranial nerve palsy	5	19%	10	33%	8	26%	23	26%
III, IV, VI	4	15%	6	20%	5	16%	15	17%
VII	0	0%	4	13%	3	10%	7	8%
IX, X,XII	1	4%	5	17%	1	3%	7	8%
Mononeuropathy (*N* = 84)	1	4%	4	13%	4	13%	9	10%
Focal amyotrophy (*N* = 84)	0	0%	4	13%	1	3%	5	6%
Hearing loss								
Bilateral normal hearing at diagnosis	22	85%	29	97%	28	90%	79	91%
Bilateral normal hearing at last review	20	77%	27	90%	25	81%	72	83%
Severe/total hearing loss in 1 ear	3	8%	2	7%	4	6%	9	2%
Hearing implant	1	4%	1	3%	1	3%		3%
Visual features								
Any eye feature binary[a]	9	34.6%	21	70.0%	23	74.2%	53	61%
logMar>1.0 in worse eye (*N* = 69)*	3	18%	6	25%	12	43%	21	30%
logMar>0.3 in better eye(*N* = 70)	3	16%	4	17%	9	32%	16	23%
logMar>1.0 in better eye (*N* = 71)	1	5%	2	8%	0	0%	3	4%
Cognitive, Behavioural and Psychological manifestations								
Developmental delay[b]	3	12%	1	4%	0	0%	4	4.7%
Attention deficit hyperactivity disorder	1	4%	0	0%	2	7%	3	3.5%
Autism Spectrum Disorder	1	4%	0	0%	2	6%	3	3.5%
Psychological issues	8	32%	6	21%	10	33%	24	29%

Table detailing NF2 features related to genetic severity group that were noted clinically or present on imaging at last review.
*$P < .05$.
[a]One or more eyes with any or the following features: lens opacity, epiretinal membrane, retinal hamartoma, amblyopia, squint/ocular mobility, diplopia, nystagmus, ptosis, optic nerve sheath meningioma, optic atrophy, papilledema, CN III tumour.
[b]Developmental delay secondary to chromosome 22 microdeletion (*N* = 2) and ring chromosome 22 (*N* = 1). Mild delay noted in one child with small intragenic deletion.

seizure was 7.1 years (range 3-11). One 2B case had a single seizure aged 1 with normal brain MRI, whereas the second had epilepsy between ages 3-16 and focal cortical dysplasia on MRI. The group 3 patients included: one with initially nocturnal, later including daytime seizures from age 6 to 12, with MRIs showing focal cortical dysplasia aged 8 and meningioma age 14; one patient with complex partial seizures from age 8, who had an arachnoid cyst, focal cortical dysplasia and subcortical signal change; one patient with seizures from age 8, who had an area of meningioangiomatosis, cortical dysplasia and cerebellar cortical dysplasia and prominent perivascular spaces; one patient who had seizures aged 11-13, which resolved after removal of an area of meningioangiomatosis/cortical dysplasia; one patient with a pilocytic astrocytoma, who had a seizure age 11; and one patient with a choroid plexus cyst and temporal lobe cortical dysplasia, who had a single seizure age 9.

3.3.4 | Hearing

In all three groups a non-statistically-significant decline was seen in hearing from diagnosis to last assessment (Table 4) with 91% having bilateral normal hearing at presentation to 83% at last review. Two young children (group 3) lost hearing unilaterally: age 4 from a cochlear nerve schwannoma and age 5 from a VS. Nine children in total had severe or total hearing loss, unilateral in 8 and bilateral in one. There was no correlation with genetic severity. Three children had a hearing implant: cochlear (ages 14 and 17) and auditory brainstem (age 11).

3.3.5 | Visual acuity

Thirty per cent of children had severe visual impairment (logmar >1.0) in one eye, with proportions significantly increasing with genetic

severity (Table 4; P = .024). Twenty-three per cent had mild visual impairment in their better seeing eye. Of group 3 patients 12 (43%) had severely affected vision in one eye, and 9 (32%) had impaired vision (LogMar 0.3 or greater) in their better seeing eye. Contributing to the visual loss included retinal hamartoma (N = 10), cataract (N = 4), epiretinal membrane (N = 3), optic nerve sheath meningioma (N = 3), suprasellar meningioma (N = 1), an optic pathway lesion (N = 1), and optic atrophy from prolonged raised intracranial pressure associated with an undiagnosed intracranial meningioma (N = 1). Overall 61% of all children had at least one NF2 eye feature with proportions rising significantly with genetic severity (P = .001).

3.3.6 | Cognitive and behavioural difficulties

Diagnosis of attention-deficit-hyperactivity-disorder(ADHD) and autistic-spectrum traits had been noted in a small proportion (3.5%

TABLE 5 Table detailing ages and numbers of key NF2 features, and tumour burden on MRI at last review, according to genetic severity (cranial MRI N = 79, spinal MRI N = 71)

	2A		2B		3		Overall	
Tumour load	**Mild**		**Moderate**		**Severe**			
Age when:	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
First head MRI*	11.5	3.5	11.2	4.0	9.8	3.3	10.8	3.7
First VS[a] detected*	12.5	3.1	12.3	3.0	10.0	3.3	11.5	3.3
Bilateral VS*	12.5	3.1	12.1	3.8	10.2	3.3	11.5	3.6
First VS >1CM	13.6	2.7	13.8	1.9	12.3	3.1	13.1	2.7
VS growth rate (cm/year)	.15	.14	.18	.23	.21	.31	.18	.23
Number of patients and % within genetic severity	*N*	Column %	*N*	Column %	*N*	Column %	*N*	Column %
VS > 1 cm at first scan	4	19%	9	39%	9	33%	22	31%
No VS*	7	27%	8	27%	6	19%	21	24%
Unilateral VS*	4	15%	0	0%	1	3%	5	6%
Bilateral VS*	15	58%	22	73%	24	77%	61	70%
Intracranial meningioma*	6	26%	11	38%	14	52%	31	38%
Non vestibular cranial schwannoma*	8	35%	17	59%	23	85%	48	61%
Spinal ependymoma*	4	19%	12	50%	11	42%	27	38%
Spinal schwannoma*	7	33%	16	67%	17	65%	40	56%
Spinal meningioma	2	10%	6	25%	5	19%	13	18%
Extradural schwannoma*	1	5%	11	46%	8	31%	20	28%
Extraspinal schwannoma*	0	0%	3	13%	6	23%	9	13%
Atypical MRI anomaly								
Number of patients with MRI anomalies*	5	22%	8	28%	17	63%	30	38%
Focal cortical dysplasia*	1	4%	4	14%	7	26%	12	15%
Cerebellar cortical dysplasia*	1	4%	2	7%	6	22%	9	11%
Brain stem or cerebellar peduncle lacunar infarcts	1	4%	1	3%	1	4%	3	4%
Abnormal choroid plexus cyst/calcification	0	0%	0	0%	2	7%	2	3%
Meningioangiomatosis	0	0%	0	0%	2	7%	2	3%
White matter hyperintensity	0	0%	1	3%	1	4%	2	3%
Prominent perivascular spaces	0	0%	1	3%	1	4%	2	3%
Chiari I malformation	0	0%	1	3%	0	0%	1	1%
Pilocytic astrocytoma of optic pathway	0	0%	0	0%	1	4%	1	1%
Frontal lobe ependymoma	1	4%	0	0%	0	0%	1	1%
Developmental venous anomaly	0	0%	1	3%	0	0%	1	1%
Cystic encephalomalacia	0	0%	0	0%	1	4%	1	1%
Cortical malformation	0	0%	0	0%	1	4%	1	1%

*P < .05.

[a]Vestibular schwannoma.

each), in keeping with population limits, however specific neurocognitive assessments were not available to confirm these diagnoses. Developmental delay was noted in 4.7% (Table 4), in 2A being attributed to chromosomal disorders: Ring Chromosome 22 associated with severe global delay; and chromosome 22 microdeletions extending beyond the *NF2* gene associated with variable delay and/or autistic-spectrum features One 2B child with a small intragenic NF2 deletion had mild delay reported.

In contrast, 24 patients (29%) had psychological issues, mostly related to low mood and anxiety. There was no relation between psychological issues and genetic severity.

3.3.7 | Atypical features

Atypical features were more common in group 3. Vascular anomalies in group 3 included one patient each with coarctation of the aorta, renal artery stenosis and a pontine infarct presenting with upper motor neurone signs age 14. A second child, with a 22q microdeletion including NF2 (2A), developed a pontine stroke secondary to vertebral artery stenosis. One child (2B) had delayed growth aged 15 and one (3) had constitutional delay of growth and puberty. Unusual eye features included one each of morning glory anomaly (3), microtropia (3), and optic nerve hypoplasia causing unilateral blindness (2A). One child each had removal of a pilomatrixoma (2A) and exostosis (2B). One child (with 22qdeletion) had sub-glotic stenosis and laryngomalacia (2A), and three had developmental delay secondary to chromosomal deletions (2A). One child had pan-hypopituitarism associated with hypothalamic, suprachiasmal meningioangiomatosis (3).

3.3.8 | Tumour burden

Reports of cranial and spinal MRI were available in 79 and 71 patients (Table 5). Table 5 illustrates the tumour load according to severity groups. Features seen on first MRI scan for group 3 children are given in Supplementary Table S1. There were significant trends across severity for tumour load ($P < .05^1$). VS size greater than 1 cm at first scan was present in 19% of 2A and 31% of the whole cohort, and not related to genetic severity. These patients were significantly older at first scan compared to those with smaller VS($t(69) = 5.25, P < .001$). There was little difference in the rate of growth of VS across severity groups (Table 5, $P = .89$).

3.3.9 | Atypical MRI features

Thirty-eight per cent of the cohort (Table 5) had an atypical MRI anomaly, with a significant trend with genetic severity ($P = .002$). Most frequently seen were focal cortical dysplasia in 12 (15%) patients (frontal lobe $N = 4$, parietal lobe $N = 3$, temporal lobe $N = 1$, area not specified $N = 4$) and cerebellar cortical dysplasia in 9 (11%), the prevalence of which increased with genetic severity ($P = .017$, $P = .024$, respectively).

3.4 | Paediatric NF2 management

3.4.1 | Interventions

Fifty-eight major interventions (VS surgery/spinal surgery/non-VS intracranial surgery/radiotherapy/bevacizumab) were performed along with 20 other treatments (Table 6). Thirty-five per cent of 2A patients underwent ≥1 major interventions, compared to 48% in group 3. In the whole cohort 37 patients (42%) had ≥1 and 14 (16%) ≥2 major interventions, increasing to 44 (50%) and 22 (25%), respectively when including all procedures. Most frequent intervention was bevacizumab (26%). Only 5 (6%) children underwent VS surgery compared to 14 (16%) each undergoing spinal surgery or non-VS intracranial surgery.

3.4.2 | Bevacizumab

Bevacizumab was given to 23 children (26%) with four centre approval, starting at a mean age of 14.9 years in 2A and 12.7 years in group 3 ($P = .008$). The indication was for rapidly growing unilateral vestibular schwannoma (UVS) in 18 and bilateral vestibular schwannoma (BVS) in 3 cases, and one each for a lumbosacral schwannoma and a cystic spinal ependymoma. In two cases surgery occurred later on the target VS.

3.4.3 | Intracranial surgery

5 (6%) children underwent VS surgery. In two cases at a young age (8 and 11), both pre 2011, before routine use of bevacizumab. Both were later given bevacizumab for growing VS; in one case after 6 years (for bilateral growth), and in the second case 1 year post-surgery (for a growing contralateral tumour). Three children had VS surgery more recently, aged 14, 15 and 18. All three also took bevacizumab; one three years post-surgery (for a growing contralateral VS), two for growing VS prior to surgery (treatment for 1 year before surgery to the same lesion age 15, and in the second case for 3 years for growing BVS, before unilateral VS surgery aged 18).

A total of 14 (16%) patients had non-VS intracranial surgery occurring in all three groups. Four surgeries (mean age 4.8 years), occurred pre-2010: for optic nerve sheath meningioma; to debulk a hypothalamic supra-chiasmal mass; to resect a symptomatic posterior fossa meningioma; and an exploratory craniotomy for a pericavernous meningioma later treated with radiotherapy. Ten surgeries occurred after 2010 (mean age 12.2 years). In 8 of these, surgery was to resect a meningioma (grade II in 5/7 cases where histology was available); one patient had resection of a grade II frontal lobe ependymoma aged 15; and one had decompression of the optic nerves. In 5/14 cases (36%) the surgery occurred at or before diagnosis of NF2 and in 12/14 (86%) cases the indication was symptoms, growth, position or size of the lesion. In three cases the indication was threat to vision (optic nerve meningioma surgery, optic nerve decompression, or resection of suprasellar meningioma encasing the optic nerve).

TABLE 6 Interventions

	2A Mild		2B Moderate		3 Severe		Overall	
Age at intervention:	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
First major intervention	11.9	4.4	11.5	3.7	10.4	3.5	11.1	3.8
Bevacizumab*	14.9	1.3	11.8	6.3	12.7	2	12.9	4.2
Non VS intracranial surgery	10.2	5.5	10.6	4.0	9.3	5.9	10.1	4.8
Spinal surgery	4		11.3	4.9	10.7	3.5	10.5	4.3
Other treatments	14.3	0.6	12	5.7	9.1	6.8	11.3	5.8
Proportion of patients having an intervention	*N*	%	*N*	%	*N*	%	*N*	%
VS surgery[a]	1	4%	3	10%	1	3%	5	6%
Radiotherapy	0	0%	2	7%	0	0%	2	2%
Spinal surgery[b]	1	4%	6	20%	7	23%	14	16%
Non-VS intracranial surgery	5	19%	5	17%	4	13%	14	16%
Bevacizumab	6	23%	8	27%	9	29%	23	26%
Other treatments:	3	12%	9	30%	8	26%	20	23%
Eye procedures (squint surgery, lid weight, patching, resection of orbital schwannoma)							9	10%
Resection of peripheral schwannomas (brachial plexus, finger, foot)							3	3%
Orthopaedic surgery (spinal fixation, epiphyodesis of knee, Achilles tendon surgery							3	3%
Insertion of shunt							2	2%
Vocal cord procedures							2	2%
Insertion of cochlear implant							1	1%
Vascular surgery (renal and aorta)							2	2%
Other							2	2%
By number of major interventions:								
0	17	65%	17	57%	16	52%	50	57%
1	6	23%	7	23%	10	32%	23	26%
2 or more	3	12%	6	20%	5	16%	14	16%
By total number of interventions:								
0	16	62%	13	43%	14	45%	43	49%
1	7	27%	7	23%	8	26%	22	25%
2 or more	3	12%	10	33%	9	29%	22	25%

*$P < .05$.

[a]5 Vestibular schwannoma S surgeries: 2 partial retrosigmoid (1 cochlear nerve preserving), 3 translabyrinth (of which: 2 were partial; 1 was cochlear nerve preserving).

[b]Spinal surgery included 2A:schwannoma (*N* = 1); 2B ependymoma (*N* = 2), meningioma (*N* = 1), schwannoma (*N* = 3); group 3 ependymoma (*N* = 3), meningioma (*N* = 2), schwannoma (*N* = 2).

3.4.4 | Spinal surgery

Other than 2 surgeries pre-2010, all occurred after the National NF2 service was established. Five were for ependymoma (mean age 11.6 years), 3 for grade 1 meningioma (mean age12.3 years) and 6 for schwannoma (mean age 10.2 years). Of the 3 ependymoma cases where histology was available all were grade II. In 7/14 (50%) surgery occurred at or before the diagnosis of NF2, due to the child presenting symptomatically from the spinal lesion (or in one case symptomatic from a synchronous intracranial lesion). In 10/12 post-2010 cases there was clear documentation of symptoms or signs arising from the lesion, or significant growth as the indication for surgery.

3.4.5 | Radiotherapy

Two 2B children underwent radiotherapy; one, aged 8, for a large bilateral optic nerve sheath meningioma severely threatening vision; and one proton beam therapy aged 15, for an intracranial meningioma inaccessible to surgery. No child had radiotherapy for VS.

4 | DISCUSSION

To raise paediatric awareness of NF2, we previously reported in detail the presenting features of the sporadic patients.[14] Including here all 87 children with NF2 in England, we present the largest series of paediatric NF2, and the first stratified by genetic severity. As the aim of the paper was to report phenotype related to severity grouping we have pooled data from both symptomatic and presymptomatic children known to have NF2. Several previous series have reported under 25 patients.[7,10,12,13,39] Evans et al reported 68 English patients aged under 16 in 1999 precluding overlap with this cohort.[11] Other than children as yet undiagnosed, this study represents almost complete ascertainment of paediatric NF2 in England and reflects current management.

The data reveal that paediatric NF2 is overwhelmingly (91%) constitutional; in contrast to all-age cohorts where 33%-58% have likely mosaic disease.[42,44] No patients were assigned group 1 (sporadic with no *NF2* path_variant identified in blood), as these patients typically present at older ages.[42] Previous guidelines recommended predictive genetic testing aged 10 in children at 50% risk for NF2, with MRI surveillance starting aged 10-12.[3,45] Only 24/49 (49%) patients with familial NF2 had a predictive genetic test, as in the remainder, NF2 features were noted before genetic testing. This data shows that for group 2B and 3 patients to have predictive testing, this would need to occur much younger than age 10, due to the early age at first manifestations. As 33% of group 3 patients had a VS > 1 cm on first scan, a feature strongly associated with later age at first scan; the recommendation for first scan age 10 is validated, and reaffirms the importance of timely diagnosis.[14]

This study illustrates the major physical and psychological impact of paediatric NF2. Although a clear trend in tumour load and intervention was apparent with severity, all groups had a significant burden of disease with need for major intervention. The significant trend in proportion with VS and other neuroaxis lesions illustrates that genotype-phenotype differences emerge from childhood, with more severe manifestations in group 3 compared to group 2A patients.

One or more seizure occurred in 19% of group 3 and 9% of the whole cohort, comparable to previous studies[5] where in 6/7 cases seizure was linked to meningioma/VS.[11] In our cohort 12 patients had cortical dysplasia of which 6 (46%) had one or more seizure. While difficult to attribute the cause of the seizure(s) an apparent association with cortical dysplasia was seen in 6/8 cases (75%). EEG recordings were unfortunately not available, but for future analyses would be helpful to delineate any causative effect of the cortical dysplasia on seizure development. Spinal lesions were more prevalent in 2B/3 patients compared to 2A, as noted previously where 17/28 (61%) patients with spinal ependymoma had truncating path_variants in exons 2-13.[4]

MRI anomalies were predominantly seen in group 3 patients, notably focal cortical dysplasia and cerebellar cortical dysplasia. The clinical significance of these features is uncertain but may suggest a role for Merlin in brain development. Vascular anomalies were seen both intracranially, previously described in detail[46] and in major vessels, and three patients had features suggestive of brainstem or cerebellar peduncle lacunar infarcts, further suggesting that vascular abnormality is a feature of NF2.

This study highlights the significant threat to vision in children also at high risk for bilateral deafness. A previous study found that 14% of childhood-onset NF2, retained visual acuity of 1.0 (equivalent to logMar 0.0) in both eyes after 12 years follow up.[6] We found that 43% of group 3 patients had severely affected vision in one eye within childhood. We have previously reported correlation of NF2 specific eye features with genetic severity.[47] As this was a retrospective review of clinical records it was not possible to ascertain to what extent each individual ophthalmic feature contributed to visual impairment, however contributing to the visual loss in our patients were both tumour related lesions such as optic nerve sheath meningioma, along with cataract, retinal hamartoma and epiretinal membrane. Given the eventual threat of multisensory impairment in these children, and the high proportion with visual problems in childhood, 1-2 yearly ophthalmic review from infancy/diagnosis is needed in 2B/3 children to minimise preventable loss of vision.

While it is unusual for NF2 related hearing loss to occur in young children, two children developed unilateral deafness very young from cochlear or VS. In a recent all age NF2 cohort 50% of severe patients were predicted to lose hearing by 32 years.[48] In the current cohort only 83% retained bilateral normal hearing at the time of the last review. This data demonstrates that exceptionally, loss of hearing in the first ear can occur from a very young age.

Most frequent interventions were bevacizumab, non-VS intracranial surgery and spinal surgery. While meningioma in NF2 is more commonly grade I, of the 10 post-2010 cases of non-VS intracranial surgery, this was for grade II lesions in the 6/8 with available histology. Furthermore resection of a grade II frontal ependymoma is atypical, as NF2 ependymoma is typically spinal.[49] Of the spinal surgery occurring post-2010 in 6/12 (50%) it occurred before NF2 specialist review, mostly for symptoms or neurological signs. In 5 cases surgery was to resect spinal ependymoma. Frequently NF2 related ependymoma are observed and may not need resection. Ideally if the diagnosis of NF2 is apparent at presentation, unless urgent surgery is needed, rapid referral and assessment by a specialist NF2 MDT prior to surgery may limit avoidable intervention.

VS surgery only occurred three times post-2010, with preference for bevacizumab in rapidly growing VS. The mean rate of VS growth did not vary with genetic severity, in keeping with previous studies.[50] It is therefore likely that the possible dominant negative effect of truncating variants acts only as a driver for tumour development and that complete loss of NF2 function occurs similarly across different genetic variants in the developed tumour thus showing no difference in growth rates. In England bevacizumab has strict eligibility criteria of 4 mm growth in 12 months. Group 3 patients commenced treatment younger than 2A patients, indicating either that rapid VS growth occurred at a younger age in group 3, or a greater willingness to start bevacizumab younger in group 3 patients, with likely more severe

disease. Use of bevacizumab did not always avoid surgery (2/21 cases had later VS resection) but likely deferred surgery in some cases.

The main limitation of this study is that as a retrospective review of routinely collected data, we were dependent on clinical record keeping, rather than utilising prospectively gathered data. A full data set was not possible for all cases such as visual acuity at presentation and last review, so we were unable to document visual loss over time. The main limitation for a natural history study is the mean follow up length of 6.5 years and mean age at last review of 13.9 years, meaning that many key outcomes such as hearing would not have been significantly affected by last review. Following this cohort prospectively, will allow us to develop a longer term dataset of NF2 natural history in these patients.

Managing NF2 is complex. This study highlights some key areas for surveillance, in addition to routine hearing and MRI. With 43% group 3 having essentially lost vision in one eye; early and frequent eye review is important to limit preventable loss of vision. With 29% reporting anxiety and low mood, psychological support is essential for children with NF2 to improve outcome. As 8% had a lower CNP, with unilateral or bilateral vocal cord or bulbar palsy, it is helpful to regularly review speech and swallow in the 2B/3 patients.

The NF2 genetic severity score allows documentation of the differing phenotypes emerging from childhood. While patients with familial NF2 will have an expectation of likely severity, those with sporadic NF2 do not have this reference point. A severity score based on genotype can in part suggest the likely future phenotype. We have collected detailed phenotypic information from all children known to have NF2 within England managed using current protocols; by further developing genotype derived natural history data the aim is that we can better inform clinicians and patients to aid NF2 management.

ACKNOWLEDGEMENTS

The authors wish to acknowledge NHS England for support of the National NF2 program and members of the English NF2 research group: Patrick Axon, Juliette Gair, Carolyn Smyth, Shazia K Afridi, Rupert Obholzer, Vanessa Everett, Nicola Jarvis, Kirsty Henshaw, C Oliver Hanemann, Wendy Howard, Anne May, Carolyn Redman, Rohini Rattihalli, Helen Tomkins. D.G.E. is supported by the all Manchester NIHR Biomedical Research Centre (IS-BRC-1215-20007).

AUTHOR CONTRIBUTIONS

Study design: D.H.,S.C., K.L., J.N., D.G.E.; acquisition, analysis and interpretation of data: D.H.,B.E.,A.P.,K.L.,M.W.,G.A.,P.P.; drafting the manuscript; D.H.,B.E.; revising manuscript critically for intellectual content: A.P., P.P.,J.N.,D.G.E.

CONFLICT OF INTEREST

DGE reports a travel grant from Astrazeneca, outside the submitted work, and SC reports personal fees from Eisai, and non-financial support from PTC Therapeutics, outside the submitted work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ENDNOTE

[1]intracranial meningioma: $P = .021$, no of Vestibular Schwannomas (0-2): $P = .013$, non-vestibular cranial schwannoma: $P = 1.37*10^{-4}$, spinal schwannoma: $P = .025$, extraspinal schwannoma: $P = .011$, spinal ependymoma ($P = .038$), extradural schwannoma ($P = .026$).

ORCID

Dorothy Halliday https://orcid.org/0000-0002-1098-8599
Beatrice Emmanouil https://orcid.org/0000-0003-1223-5571

REFERENCES

1. Rouleau GA, Merel P, Lutchman M, et al. Alteration in a new gene encoding a putative membrane-organizing protein causes neurofibromatosis type 2. *Nature*. 1993;363(6429):515-521.
2. Evans DG, Bowers NL, Tobi S, et al. Schwannomatosis: a genetic and epidemiological study. *J Neurol Neurosurg Psychiatry*. 2018;89(11):1215-1219.
3. Evans DG, Baser ME, O'Reilly B, et al. Management of the patient and family with neurofibromatosis 2: a consensus conference statement. *Br J Neurosurg*. 2005;19(1):5-12.
4. Plotkin SR, O'Donnell CC, Curry WT, Bove CM, MacCollin M, Nunes FP. Spinal ependymomas in neurofibromatosis type 2: a retrospective analysis of 55 patients. *J Neurosurg Spine*. 2011;14(4):543-547.
5. Evans DGR, Huson SM, Donnai D, et al. A clinical study of type 2 neurofibromatosis. *QJM*. 1992;84(1):603.
6. Bosch MM, Boltshauser E, Harpes P, Landau K. Ophthalmologic findings and long-term course in patients with neurofibromatosis type 2. *Am J Ophthalmol*. 2006;141(6):1068-1077.
7. Mautner VF, Tatagiba M, Guthoff R, Samii M, Pulst SM. Neurofibromatosis 2 in the pediatric age group. *Neurosurgery*. 1993;33(1):92-96.
8. Evans DG, Freeman S, Gokhale C, et al. Bilateral vestibular schwannomas in older patients: NF2 or chance?*J Med Genet*. 2015;52(6):422-424.
9. Ruggieri M, Gabriele AL, Polizzi A, et al. Natural history of neurofibromatosis type 2 with onset before the age of 1 year. *Neurogenetics*. 2013;14(2):89-98.
10. MacCollin M, Mautner VF. The diagnosis and management of neurofibromatosis 2 in childhood. *Semin Pediatr Neurol*. 1998;5(4):243-252.
11. Evans DG, Birch JM, Ramsden RT. Paediatric presentation of type 2 neurofibromatosis. *Arch Dis Child*. 1999;81(6):496-499.
12. Nunes F, MacCollin M. Neurofibromatosis 2 in the pediatric population. *J Child Neurol*. 2003;18(10):718-724.
13. Ruggieri M, Iannetti P, Polizzi A, et al. Earliest clinical manifestations and natural history of neurofibromatosis type 2 (NF2) in childhood: a study of 24 patients. *Neuropediatrics*. 2005;36(1):21-34.
14. Anand G, Vasallo G, Spanou M, et al. Diagnosis of sporadic neurofibromatosis type 2 in the paediatric population. *Arch Dis Child*. 2018;103(5):463-469.
15. Baser ME, Friedman JM, Aeschliman D, et al. Predictors of the risk of mortality in neurofibromatosis 2. *Am J Hum Genet*. 2002;71(4):715-723.

16. Ferner RE, Shaw A, Evans DG, et al. Longitudinal evaluation of quality of life in 288 patients with neurofibromatosis 2. *J Neurol*. 2014;261(5):963-969.
17. Patel CM, Ferner R, Grunfeld EA. A qualitative study of the impact of living with neurofibromatosis type 2. *Psychol Health Med*. 2011;16(1):19-28.
18. Hexter A, Jones A, Joe H, et al. Clinical and molecular predictors of mortality in neurofibromatosis 2: a UKnational analysis of 1192 patients. *J Med Genet*. 2015;52(10):699-705.
19. Smith MJ, Urquhart JE, Harkness EF, et al. The contribution of whole gene deletions and large rearrangements to the mutation Spectrum in inherited tumor predisposing syndromes. *Hum Mutat*. 2016;37(3):250-256.
20. Smith MJ, Higgs JE, Bowers NL, et al. Cranial meningiomas in 411 neurofibromatosis type 2 (NF2) patients with proven gene mutations: clear positional effect of mutations, but absence of female severity effect on age at onset. *J Med Genet*. 2011;48(4):261-265.
21. Sainio M, Jääskeläinen J, Pihlaja H, Carpén O. Mild familial neurofibromatosis 2 associates with expression of merlin with altered COOH-terminus. *Neurology*. 2000;54(5):1132-1138.
22. Selvanathan SK, Shenton A, Ferner R, et al. Further genotype – phenotype correlations in neurofibromatosis 2. *Clin Genet*. 2010;77(2):163-170.
23. Baser ME, Kuramoto L, Joe H, et al. Genotype-phenotype correlations for nervous system tumors in neurofibromatosis 2: a population-based study. *Am J Hum Genet*. 2004;75(2):231-239.
24. Kluwe L, Bayer S, Baser ME, et al. Identification of NF2 germ-line mutations and comparison with neurofibromatosis 2 phenotypes. *Hum Genet*. 1996;98(5):534-538.
25. Evans DG, Truerman L, Wallace A, Collins S, Strachan T. Genotype/-phenotype correlations in type 2 neurofibromatosis (NF2): evidence for more severe disease associated with truncating mutations. *J Med Genet*. 1998;35:450-455.
26. Ruttledge MH, Andermann AA, Phelan CM, et al. Type of mutation in the neurofibromatosis type 2 gene (NF2) frequently determines severity of disease. *Am J Hum Genet*. 1996;59(2):331-342.
27. Kluwe L, Mautner VF. Mosaicism in sporadic neurofibromatosis 2 patients. *Hum Mol Genet*. 1998;7(13):2051-2055.
28. Kluwe L, MacCollin M, Tatagiba M, et al. Phenotypic variability associated with 14 splice-site mutations in the NF2 gene. *Am J Med Genet*. 1998;77(3):228-233.
29. Evans DG, Bowers N, Huson SM, Wallace A. Mutation type and position varies between mosaic and inherited NF2 and correlates with disease severity. *Clin Genet*. 2013;83(6):594-595.
30. Neary WJ, Stephens D, Ramsden RT, Evans G. Psychosocial effects of neurofibromatosis type 2 (part 1): general effects. *Audiolog Med*. 2006;4(4):202-210.
31. Lloyd SKW, King AT, Rutherford SA, et al. Hearing optimisation in neurofibromatosis type 2: a systematic review. *Clin Otolaryngol*. 2017;42(6):1329-1337.
32. Ruggieri M, Pratico AD, Evans DG. Diagnosis, management, and new therapeutic options in childhood neurofibromatosis type 2 and related forms. *Semin Pediatr Neurol*. 2015;22(4):240-258.
33. King AT, Rutherford SA, Hammerbeck-Ward C, et al. High-grade glioma is not a feature of neurofibromatosis type 2 in the unirradiated patient. *Neurosurgery*. 2018;83(2):193-196.
34. Morris KA, Golding JF, Blesing C, et al. Toxicity profile of bevacizumab in the UKneurofibromatosis type 2 cohort. *J Neurooncol*. 2017;131(1):117-124.
35. Slusarz KM, Merker VL, Muzikansky A, Francis SA, Plotkin SR. Long-term toxicity of bevacizumab therapy in neurofibromatosis 2 patients. *Cancer Chemother Pharmacol*. 2014;73(6):1197-1204.
36. Goutagny S, Giovannini M, Kalamarides M. A 4-year phase II study of everolimus in NF2 patients with growing vestibular schwannomas. *J Neurooncol*. 2017;133(2):443-445.
37. Fisher LM, Doherty JK, Lev MH, Slattery W3rd. Concordance of bilateral vestibular schwnannoma growth and hearing changes in neurofibromatosis 2: neurofibromatosis 2 natural history consortium. *Otol Neurotol*. 2009;30:835-841.
38. Mautner VF, Lindenau M, Baser ME, Kluwe L, Gottschalk J. Skin abnormalities in neurofibromatosis 2. *Arch Dermatol*. 1997;133(12):1539-1543.
39. Matsuo M, Ohno K, Ohtsuka F. Characterization of early onset neurofibromatosis type 2. *Brain Dev*. 2014;36(2):148-152.
40. Goutagny S, Bah AB, Henin D, et al. Long-termfollow-up of 287 meningiomas in neurofibromatosis type 2 patients: clinical, radiological, and molecular features. *Neuro Oncol*. 2012;14(8):1090-1096.
41. Aboukais R, Zairi F, Bonne NX, et al. Causes of mortality in neurofibromatosis type 2. *Br J Neurosurg*. 2015;29(1):37-40.
42. Halliday D, Emmanouil B, Pretorius P, et al. Genetic severity score predicts clinical phenotype in NF2. *J Med Genet*. 2017;54(10):657-664.
43. Lloyd SK, Evans DG. Neurofibromatosis type 2 service delivery in England. *Neurochirurgie*. 2018;64(5):375-380.
44. Evans DG, Ramsden RT, Shenton A, et al. Mosaicism in neurofibromatosis type 2: an update of risk based on uni/bilaterality of vestibular schwannoma at presentation and sensitive mutation analysis including multiple ligation-dependent probe amplification. *J Med Genet*. 2007;44(7):424-428.
45. Evans DG, Raymond FL, Barwell JG, Halliday D. Genetic testing and screening of individuals at risk of NF2. *Clin Genet*. 2012;82(5):416-424.
46. Lascelles K, Afridi S, Siddiqui A, Hemingway C, Ferner R, Ganesan V. Cerebral vasculopathy in childhood neurofibromatosis type 2: cause for concern?*Dev Med Child Neurol*. 2018;60(12):1285-1288.
47. Painter SL, Sipkova Z, Emmanouil B, Halliday D, Parry A, Elston JS. Neurofibromatosis type 2-related eye disease correlated with genetic severity type. *J Neuroophthalmol*. 2019;39(1):44-49.
48. Emmanouil B, Houston R, May A, et al. Progression of hearing loss in Neurofibromatosis type 2 according to genetic severity *Laryngoscope*. 2019;129(4):974-980.
49. Lee CH, Chung CK, Kim CH. Genetic differences on intracranial versus spinal cord ependymal tumors: a meta-analysis of genetic researches. *Eur Spine J*. 2016;25(12):3942-3951.
50. Mautner VF, Baser ME, Thakkar SD, Feigen UM, Friedman JM, Kluwe L. Vestibular schwannoma growth in patients with neurofibromatosis type 2: a longitudinal study. *J Neurosurg*. 2002;96(2):223-228.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Halliday D, Emmanouil B, Vassallo G, et al. Trends in phenotype in the English paediatric neurofibromatosis type 2 cohort stratified by genetic severity. *Clin Genet*. 2019;96:151–162. https://doi.org/10.1111/cge.13551